Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	LINQ QT Study
Clinical Investigation Plan Identifier	MDT CTMS Protocol # **MDT22018**
Study Product Name	LINQ™ and LINQII™ Insertable Cardiac Monitor (ICM) System
Sponsor/Local Sponsor	Medtronic CRM 8200 Coral Sea Street NE Mounds View, MN 55112
Document Version	2.0
Version Date	21 SEP 2022
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1. Glossary

Term	Definition
AE	Adverse Event
MyCareLink®	Network (registered trademark of Medtronic) designed to receive and store transmitted LINQ™/LINQII™ ICM data
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Cardiovascular
eCRF	Electronic Case Report Form
EC/IRB/HREB/Ethics Board	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICD	Implantable Cardiac Defibrillator
ICF	Informed Consent Form
ICM	Insertable Cardiac Monitor
ms	milliseconds
SAE	Serious Adverse Event
VitalPatch® RTM	External, wearable patch (registered trademark of Vital Connect, Inc.) that provides up to 7 days of monitoring in order to monitor parameters such as ECG, heart rate variability, respiratory rate, temperature, activity, and posture.

2. Synopsis

Title	LINQ QT Study
Clinical Study Type	Prospective, non-randomized, multi-center, observational, post-market clinical study.
Product Name	LINQ™, LINQII™
Sponsor	Medtronic 8200 Coral Sea Street NE Mounds View, MN 55112
Local Sponsor	Medtronic Research and Technology 8200 Coral Sea Street NE Mounds View, MN 55112
Indication under investigation	QT interval changes due to antiarrhythmic drug loading
Investigation Purpose	The purpose of this study is to determine if QT interval changes are detected during and after antiarrhythmic drug loading by the designed QT detection algorithm from LINQ™/LINQII™ ECG. The QT intervals before and after antiarrhythmic loading will be compared for all patients to analyze QT changes that may be caused due to antiarrhythmic drugs.
Product Status	Market-Released
Primary Objective(s) and/or Endpoint(s)s	The primary objective of the study is to determine if QT changes can be detected from LINQ™ ECG that may occur during and after antiarrhythmic loading. The QT intervals before and after antiarrhythmic loading will be compared for all patients to analyze QT changes that may be caused due to antiarrhythmic drugs.
Study Design	The LINQ™ QT Study is a prospective, non-randomized, multi-center, observational, post-market clinical study.
Randomization	Non-randomized
Sample Size	The study is expected to be conducted at up to three study sites located in the United States and will enroll up to twenty study subjects. It is anticipated that if one study site cannot enroll at least 3 subjects per month, that additional study sites will be included to meet the total enrollment target of twenty subjects.
Inclusion/Exclusion Criteria	Inclusion Criteria: • Patients implanted with LINQ™/LINQII™ prior to the study enrollment (no more than 50% patients implanted with LINQII™), but no greater than 2 years for LINQ™ or 3 years for LINQII™, or patients who are indicated to receive a LINQ™/LINQII™ implant at least 7 days prior to antiarrhythmic drug loading • Patients who are scheduled to receive antiarrhythmic drug loading • Up to 20% of patients enrolled in the study can have permanent and persistent AF • Age 18-80 • Patient is willing and able to comply with the protocol, including follow-up visits, and performing Holter recordings and patient activation transmissions

<table>
<tr><td></td><td>Exclusion Criteria:
Patients who have a contraindication to long-term antiarrhythmic therapy
Patients not suitable for long-term antiarrhythmic therapy
Patients with a previous, existing cardiac implantation (i.e., cardiac pacemaker or cardiac resynchronization requiring > 40% pacing, implantable cardioverter defibrillator (ICDs))
Co-enrollment in another study or planning to participate in a concurrent device study during the course of this clinical study that could confound the results</td></tr>
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<tr><td>Serious, Cardiovascular-related Adverse Events</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Study deviations</td><td colspan="4">Report upon occurrence</td></tr>
</table>
</td></tr>
<tr><td>Safety Assessments</td><td>There are no defined safety endpoints in the LINQ QT study as the purpose of the study is not to demonstrate safety or effectiveness. Cardiovascular-related (CV) adverse events that</td></tr>
</table>

	result in hospitalization due to anti-arrhythmic loading will be collected throughout the duration of the subject's participation in the study, beginning after the initial in-hospital/out-patient anti-arrhythmic loading.
Statistics	Since the study will be exploratory in nature and the study objectives are descriptive, no clinical endpoints will be developed. LINQ™/LINQII™ derived data will be summarized using descriptive statistics.

3. Introduction

3.1 Background

The QT interval on the electrocardiogram (ECG) has gained clinical importance, primarily because prolongation of this interval can predispose to a potentially fatal ventricular arrhythmia known as torsades de pointes, which could in turn lead to sudden cardiac death [1]. Multiple factors have been implicated in causing QT prolongation and torsades de pointes. Among these, an important risk factor for long QT syndrome is the use of QT prolonging drugs. A QT interval greater than 500 milliseconds (ms) has been shown to correlate with higher risk of torsades de pointes.

There are several commonly used medications that could lengthen QT and cause QT prolongation. One such class of medications are antiarrhythmic drugs which are used to treat heart rhythm disorders. These drugs are frequently prescribed in everyday clinical practice for the management of atrial fibrillation (AF) that affects nearly 1–2% of the general population [2,3]. The commonly used antiarrhythmics for AF rhythm control management belong to Vaughan Williams' classes, Ic and III. Both these medication categories are well known to influence ventricular depolarization and repolarization, alter QT and corrected QT interval (QTc) intervals on surface ECG and affect to variable extents the left ventricular (LV) function [4–10].

There are several studies which have assessed the effect of antiarrhythmic drugs on QT interval prolongation. One such study [11] revealed significant QTmax and QTc interval prolongation following Sotalol (from 424 ± 40 ms to 460 ± 57 ms and from 446 ± 35 ms to 474 ± 48 ms, respectively, both $p < 0.01$) and Amiodarone (from 437 ± 41 ms to 504 ± 39 ms and from 469 ± 35 ms to 527 ± 50 ms, respectively, both $p < 0.01$). Another study [12] revealed a significant mortality benefit when dofetilide was used in patients with baseline QTc intervals less than 429 ms (risk ratio 0.3), while an increase in mortality was seen with dofetilide therapy in patients with baseline QTc intervals greater than 429 ms (risk ratio 1.3) [13].

Currently, there is no reliable way for continuous and long-term monitoring of QT intervals in patients undergoing antiarrhythmics drug loading. An implantable cardiac monitor which can continuously monitor QT intervals in patients taking QT prolonging drugs can enable clinicians to track day-to-day variability in the QT intervals and also study long-term QT trends in patients.

The Reveal LINQ™ and LINQII™ devices are small, leadless cardiac monitoring systems that can be inserted subcutaneously in the chest with a minimally invasive procedure and provide continuous monitoring of diagnostic parameters for up to 3 years and 4 years respectively. An algorithm [14] has been developed and validated which can continuously measure QT intervals for every beat using LINQ™ ECG. This study is aimed at determining if QT interval changes can be detected during and after antiarrhythmic drug loading by the designed QT detection algorithm from LINQ™ ECG.

3.2 Purpose

The purpose of this study is to determine if QT interval changes are detected during and after antiarrhythmic drug loading by the designed QT detection algorithm from LINQ™ ECG. The QT intervals before and after antiarrhythmic loading will be compared for all patients to analyze QT changes that may be caused due to antiarrhythmic drugs.

4. Objectives and/or Endpoints

4.1 Objectives

4.1.1 Primary Objective

The primary objective of the study is to determine if QT changes can be detected from LINQ™ ECG that may occur during and after antiarrhythmic loading. The QT intervals before and after antiarrhythmic loading will be compared for all patients to analyze QT changes that may be caused due to antiarrhythmic drugs.

5. Study Design

The LINQ™ QT Study is a prospective, non-randomized, multi-center, observational, post-market clinical study. The study is expected to be conducted at up to three study sites located in the United States and will enroll up to twenty study subjects. It is anticipated that if one study site cannot enroll at least 3 subjects per month, then additional study sites will be included to meet the total enrollment target of twenty subjects.

Study subjects implanted with LINQ™/LINQII™ (no more than 50% patients implanted with LINQII™), but no greater than 2 years for LINQ™ or 3 years for LINQII™, or patients who are indicated to receive a LINQ™/LINQII™ implant at least 7 days prior to antiarrhythmic drug loading will be considered for enrollment in this study.

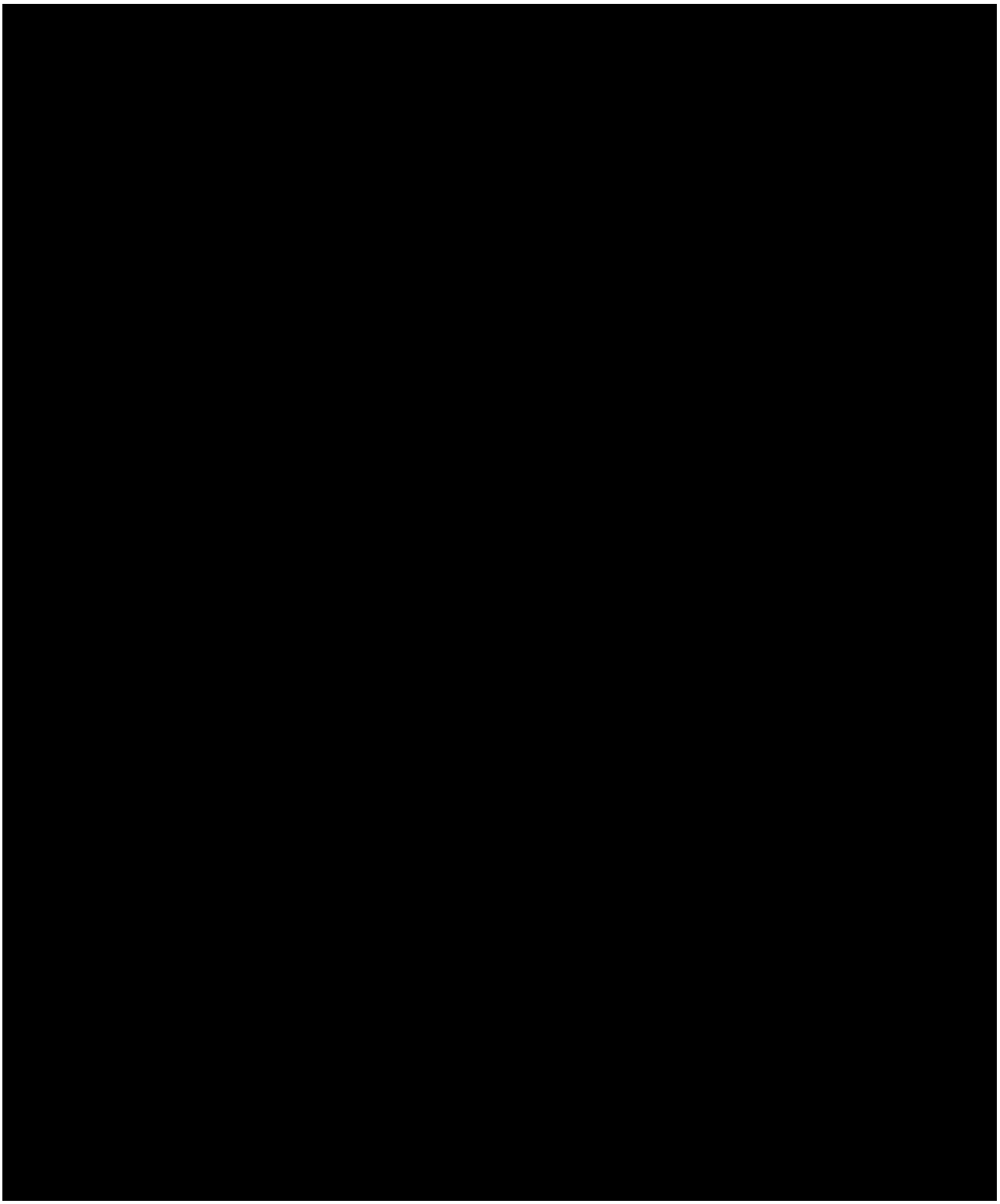

Figure 1: Study Flow Diagram

I. Index Antiarrhythmic Loading Event

1. Subjects with LINQ™ Implants

[redacted]

2. Subjects with LINQII™ Implants

[redacted]

II. Follow up period

[redacted]

[redacted]

III. Follow up clinic visits

1. Subjects with LINQ™ Implants

[redacted]

2. Subjects with LINQII™ Implants

[redacted]

5.1 Duration

Subjects will be followed until their 90 -day visit or until official study closure defined as when study data requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or by a decision by Medtronic or the applicable external parties (i.e., IRB/Ethics Committee (EC) Regulatory Authority) whichever occurs first. The estimated total study duration is approximately 13 months, representing a 7-month enrollment period, at least 3 months of follow-up per subject and at least 3 months for data analysis.

5.2 Rationale

Safety will not be a primary focus of this study as 1) the study is only collecting observational data, 2) data collected will not be used to manage the treatment of subjects in the study, 3) data collection procedures other than those related to the LINQ™/LINQII™ are not outside standard of care and 4) the safety profile of LINQ™/LINQII™ is already well known.

6. Product Description

6.1 General

The Medtronic LINQ™/LINQII™ ICM is an approved, programmable device that continuously monitors a patient's electrocardiogram (ECG) and other physiological parameters. The device records cardiac information in response to automatically detected arrhythmias and patient activation. The LINQ™/LINQII™ device is indicated in the following:

US Indications:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias.
- Patients who experience transient symptoms such as dizziness, palpitation, syncope and chest pain that may suggest a cardiac arrhythmia.

The study will be conducted using the components described in Table 1 below. All components of the LINQ™/LINQII™ system are manufactured by Medtronic, Inc. Instructions for use of the devices used in this study are provided within their respective manuals.

Table 1: Study Components

Model Number	Component	Manufacturer	Investigational or Market-released
LINQ™/LINQII™	Reveal LINQ™/LINQII™ Insertable Cardiac Monitor	Medtronic	Market-Released
SW026	2090 Programmer	Medtronic	Market-Released
MSW002 IOS (Apple)	LINQ™ Mobile Manager (LMM)	Medtronic	Market-Released
MSW003 (Android) MSW004 IOS (Apple)	My CareLink Heart™ App	Medtronic	Market-Released
24960	MyCareLink Relay™ Home Communicator	Medtronic	Market-Released
PA96000	Patient Assistant	Medtronic	Market-Released
24950	MyCareLink® Home Monitor	Medtronic	Market-Released
DR220	Holter	NorthEast Monitoring, Inc.	Market-Released

Descriptions of each component of the system are provided in the sections below.

6.1.1 Reveal LINQ™/LINQII™ II Insertable Cardiac Monitor (ICM)

The Reveal LINQ™/LINQII™ ICM is a small, leadless device that is inserted under the skin, in the chest. A specific recommended location is provided within the product manual. The device uses two electrodes on the body of the device to continuously monitor the patient's subcutaneous ECG. The device can store up to 30 min of ECG recordings from the patient-activated episodes and up to 27 min of ECG recordings from the automatically detected arrhythmias. Documentation of episode occurrence will be retained.

Figure 2: Reveal LINQ™/LINQII™ ICM

6.1.2 2090 Programmer

The Medtronic CareLink® Programmer is used to program the Reveal LINQ™/LINQII™ ICM to detect arrhythmias with various pre-specified characteristics. In addition, the programmer allows the physician to view, save, and print the ECG records currently held within the Reveal LINQ™/LINQII™ ICM.

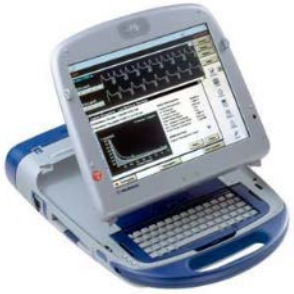

Figure 3: Medtronic 2090 Programmer

6.1.3 LINQ™ Mobile Manager (LMM) and Patient Connector Head

The Reveal LINQ™ Mobile Manager (LMM) clinician app is an application downloaded onto the clinic's tablet that communicates with the LINQII™ ICM using BLE (the tablet downloaded with the clinician app is also referred to as the "LMM" within this document). The LMM provides the operator an interface to change device settings (programming), interrogate the collected data, and display real-time data such as ECG, telemetered EGM and Marker Channel information. The LMM can also be used to assess the system. The LMM uses the 24967 Patient Connector Head for communication.

6.1.4. My CareLink Heart™ App

The MyCareLink Heart™ mobile app (also referred to as "patient app") is an application downloaded onto the patient's smartphone/tablet (Android or IOS). The patient app installed on a mobile device transfers encrypted ICM device data between the inserted LINQ II™ device and the CareLink® Network. The patient interacts with the patient app for initial setup, viewing status information, and recording symptoms. The patient app can be enabled to record cardiac information in the LINQ II™ ICM while the patient is experiencing symptoms or immediately after a symptomatic event. The clinician uses the recorded information to determine if the symptoms were associated with a cardiac event.

6.1.5. MyCareLink Relay™ Home Communicator

The MyCareLink Relay™ Home Communicator (also referred to as "home communicator") is a stationary device that transfers encrypted data from/to the patient's inserted LINQ II™ device to the CareLink® Network for patients unwilling or unable to use a smartphone/tablet. Data communication is via Bluetooth Low Energy (BLE) to the LINQ II™ ICM and wireless GSM network to the CareLink® Network.

6.1.6 Patient Assistant

The Patient Assistant is a hand-held, battery-operated telemetry device that enables the subject, on experiencing symptoms potentially indicative of a cardiac event, to manually trigger the LINQ™ ICM to collect and store an ECG record.

The Reveal Patient Assistant is intended for unsupervised patient use away from a hospital or clinic. The Patient Assistant activates the data management feature in the Reveal LINQ™ ICM to initiate recording of cardiac event data in the implanted device memory.

The subjects will be asked to press the Patient Assistant whenever they experience increased difficulty of breathing not related to an activity.

Figure 4: Patient Assistant

6.1.7 MyCareLink® Home Monitor

The MyCareLink® Home Monitor is a device that enables the device diagnostic data (which includes ECG data) to be transmitted directly from the implanted Reveal LINQ™ device to the Medtronic CareLink® Network for review by the physician.

Figure 5: MyCareLink® Patient Monitor

6.1.8 DR 220 Holter Monitor

The NorthEast Monitoring, Inc. DR220 Digital Recorder is a Holter monitor that is commercially available and designed to facilitate the ambulatory cardiac monitoring of those subjects who may benefit from such monitoring on the order of a physician, including but not limited to those with complaints of palpitations, syncope, chest pains, shortness of breath, or those who need to be monitored to judge their current cardiac function, such as subjects who have recently received pacemakers. The DR220 Digital Recorder is intended for use with Medtronic System-B compatible implantable pulse generators, implantable cardiac defibrillators, cardiac resynchronization therapy devices and implantable cardiac monitors. A Holter monitor is an external box used to record electrical heart signals from electrode patches attached to the skin (ECG) as well as from the cardiac device (EGM). There are no contraindications for the use of a DR220 Holter monitor. The Holter monitor will be used in accordance with its labeling. Only trained study personnel should apply the monitors.

The data obtained by monitoring is not analyzed at the time of recording. After the recording is complete, the data must later be downloaded to a compatible NorthEast Monitoring, Inc. Holter analysis system to be analyzed. No personal information will be entered and collected by DR220 recorder.

The DR220 Holter Recorder used in this study is a portable ECG device able to collect telemetry signals and marker channel information from any Medtronic device for up to 48 hours. The Holter Recorder has application for any subject with a Medtronic ICM. For the purposes of this study, the intended use of the Holter Recorder is to collect LINQ™ ECG recordings in order to measure QT intervals.

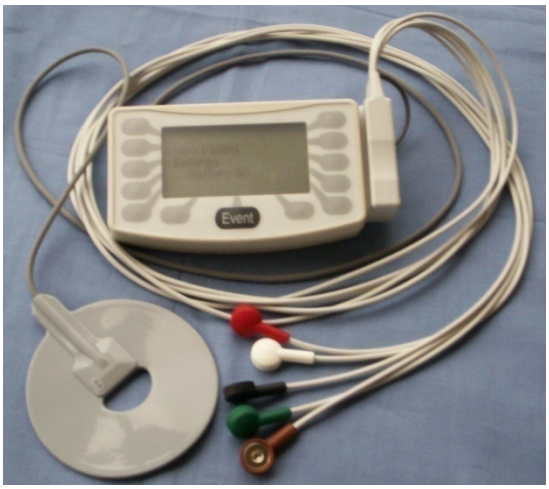

Figure 6: DR220 Holter

6.2 Shipment of Study Components

Medtronic will only allow shipment of the study device and components to the hospital or investigator when Medtronic has received all required documentation and has notified the site of readiness. Products shall be used in these centers only and according to the CIP. Clinical that are used for purposes of the study only will be provided at no cost by Medtronic. Distribution of the study device and components to centers during the study will be managed by Medtronic.

6.3 Product Accountability

Commercially available product supply will be managed in a manner consistent with other market-released products.

All products used in this study will be market released in the geographies they are used. Device Traceability may be required per local laws and regulations. If there are additional local requirements related to the LINQ QT study components beyond what is collected by Medtronic on the eCRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the study, lot, or batch number).

7. Selection of Subjects

7.1 Study Population

The subject population for the LINQ QT Study are patients implanted with LINQ™/LINQII™ prior to the study enrollment (no more than 50% patients implanted with LINQII™), but no greater than 2 years for LINQ™ or 3 years for LINQII™, or patients who are indicated to receive a LINQ™/LINQII™ implant at least 7 days prior to antiarrhythmic drug loading and who are scheduled to receive an antiarrhythmic drug loading, may undergo this study.

7.2 Subject Enrollment

Ethics Board/IRB and Medtronic approval of this Clinical Investigation Plan, the informed consent form and any other applicable documents must be obtained prior to enrolling subjects in the study. Medtronic will provide each study center with documentation of study center/investigator readiness; this letter must be received prior to subject enrollment.

When a patient and the principal investigator or authorized designee, as required, have personally signed and dated the informed consent form, the patient is considered a subject enrolled in the study. Subjects must provide informed consent before any study related procedures occur. The date the subject signed the informed consent form and data protection authorization as required by local law must be documented in the subject's medical records.

7.3 Inclusion Criteria

- Patients implanted with LINQ™/LINQII™ prior to the study enrollment (no more than 50% patients implanted with LINQII™), but no greater than 2 years for LINQ™ or 3 years for LINQII™, or patients who are indicated to receive a LINQ™/LINQII™ implant at least 7 days prior to antiarrhythmic drug loading
- Patients who are scheduled to receive antiarrhythmic drug loading
- Up to 20% of patients enrolled in the study can have permanent and persistent AF
- Age 18-80
- Patient is willing and able to comply with the protocol, including follow-up visits, and performing Holter recordings and patient activation transmissions

7.4 Exclusion Criteria

- Patients who have a contraindication to long-term antiarrhythmic therapy
- Patients not suitable for long-term antiarrhythmic therapy
- Patients with a previous, existing cardiac implantation (i.e., cardiac pacemaker or cardiac resynchronization requiring > 40% pacing, implantable cardioverter defibrillator (ICDs))
- Co-enrollment in another study or planning to participate in a concurrent device study during the course of this clinical study that could confound the results

8. Study Procedures

8.1 Schedule of Events

A patient will be considered enrolled in the study once they sign and date the Informed Consent. The subjects will be followed at in-office visits during study participation. In addition, the subjects will be completing daily manual device transmissions. The requirements for data collection and study procedures by visit are summarized in Table 2 below.

8.2 Data Collection

Data collection requirements are summarized in Table 2 below.

Table 2: Data collection and study procedure requirements at subject visits

[redacted]

8.3 Subject Screening

Subjects will be screened to ensure they meet all the inclusion criteria and none of the exclusion criteria prior to study enrollment. The subject will be considered enrolled after both the subject and the investigator (or authorized designee as required by the informed consent form [ICF]) have each personally signed and dated the ICF.

8.4 Subject Consent

The ICF is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an ICF and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's Institutional Review Board/Ethics Committee (IRB/EC) and signed and dated by the subject.

Investigators shall consider all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, approval of the CIP, ICF, and any other written study information to be provided to the subjects must have been obtained from each site's IRB/EC. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) were approved by the IRB/EC. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the IRB/EC reviewing the application prior to enrolling the subject.

The investigator must notify the subject of any significant new findings about the study that become available during the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

The informed consent form template will be sent under a separate cover.

Prior to initiation of any study-specific procedures, informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The informed consent process must be conducted by the principal investigator or his/her authorized designee, and the ICF and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject in a language, he/she is able to read and understand. The process of obtaining informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other site personnel. The informed consent process shall not waive or appear to waive subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject acknowledging that their participation is voluntary and signed and personally dated by the investigator or authorized designee as required by the ICF. If applicable, the witness shall also sign and personally date the ICF to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject.

If informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, a witnessed (impartial third party) informed consent will be allowed. In this situation, an independent witness must be present throughout the informed consent process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject. The subject should "make his/her mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The witness must also sign and personally date the ICF attesting that the information was accurately explained, and that informed consent was freely given. Detailed documentation of the consent process must be recorded in the subject's case history. The ICF should document a supervised oral process was used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The ICF and Authorization to Use and Disclose Personal Health information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the Reveal LINQ™/LINQII™ ICM insertion procedure must be able to review the subject's original signed and dated ICF and verify its completeness prior to proceeding with the insertion. In the event the Medtronic Field personnel identify informed consent as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.5 Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject (or the subject's authorized/designated representative or guardian) signed the IC and Data Protection

Authorization, as required by law, must be documented in the subject's medical records. Enrollment can occur no greater than 2 years after a LINQ™ implant, or no greater than 3 years for LINQII™. Subjects can also be enrolled who will be receiving a LINQ™/LINQII™ implant at least 7 days prior to anti-arrhythmic drug loading.

8.6 Baseline

[redacted]

8.7 Index Antiarrhythmic Loading Event

1. **Subjects with LINQ™ Implants**

[redacted]

[redacted]

2. **Subjects with LINQII™ Implants**

[redacted]

8.8 Follow-up Visits

1. **Subjects with LINQ™ Implants**

[redacted]

[redacted]

2. **Subjects with LINQII™ Implants**

[redacted]

NOTE: Subjects may be compensated for completing the required daily activations.

8.9 Nightly CareLink Data Transmissions

[redacted]

8.10 Recording Data

[redacted]

8.11 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement. If an infringement remains unresolved, multiple deviations need not be completed.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, right or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the study deviation e-CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation description and reason for deviation must be recorded. Multiple deviations of the same type at the same visit may be reported on one e-CRF.

In the event the deviation involves a failure to obtain a subject's consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations must comply with IRB/EC

policies and/or local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Table 12 for geography specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the Clinical Investigation Plan, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

8.12 Subject Exit, Withdrawal or Discontinuation

Study exit is defined as the moment when a subject officially stops participating in the study. Subjects will be considered exited upon completion of the study exit e-CRF. Prior to exiting a subject from the study, it is recommended to follow the subject until any ongoing AEs are resolved/unresolved with no further actions planned, or until official study closure, whichever occurs first. The date and reason for subject exit must be reported to Medtronic at the earliest opportunity via eCRF. Exited subjects will not be replaced. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis. Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject did not meet inclusion/exclusion criteria
- LINQ™/LINQII™ ICM explanted and not replaced with a new LINQ™/LINQII™ ICM (e.g., diagnosis determined, suspected infection, subject request, physician determination)
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator chooses to withdraw a subject (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- Subject lost to follow-up
- Death
- Study completion or termination

The following information/procedure is to be collected/performed at study exit:

- Date of exit
- Reason for exit

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB/EC.

9. Risks and Benefits

9.1 Potential Risks

There are no incremental risks introduced to the subject as a result of participation in this study.

9.2 Risk Minimization

Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP.

9.3 Potential Benefits

The LINQ QT Study may offer no direct personal benefit to individual subjects.

10. Adverse Events and Complaint Reporting

All products used are approved, not investigational and the purpose of the LINQ QT study is not to demonstrate safety or effectiveness. Cardiovascular-related or serious adverse events that result in a hospitalization due to anti-arrhythmic loading will be collected throughout out the duration of the subject's participation in the study, beginning after the initial in-hospital/out-patient anti-arrhythmic loading. Deaths will not be collected unless it resulted in a CV-related hospitalization related to the anti-arrhythmic loading.

10.1 Definitions/Classifications

For the purposes of clinical report, event definitions align with the International Organization for Standardization standard 14155 (ISO 14155). Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2020 definitions. The study will follow the definitions, however, is not claiming full compliance to ISO 14155:2020.

Table 3: Adverse Event Definitions

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2020, 3.2)
Relatedness	

Cardiovascular Related	An adverse event relating to the heart and the blood vessels or the circulation (e.g., atrial fibrillation, myocardial infarction, stroke, peripheral vascular disease, heart failure).
Seriousness	
Serious Adverse Event (SAE) (ISO 14155)	Adverse event that led to any of the following a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2020, 3.45)
Other	
Hospitalization	A therapeutic inpatient hospitalization (excludes observation unit, emergency room and outpatient visits) lasting greater than or equal to 24 hours.

10.2 Reporting of Adverse Events

Cardiovascular-related, serious adverse events will be reported on the AE eCRF, including a description of the event, the diagnosis, the date of event onset, the date the site became aware of the event, the diagnostic tests and procedures performed, actions taken as a result of the event, and outcome of the event. [redacted]. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

For all reportable events, initial reporting may be done by phone, fax, or on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

For any changes in status of a previously reported adverse event (i.e., change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or study closure, whichever occurs first.

10.2.1 Adverse Event Classification

[redacted]

AEs will be classified according to the standard definitions as outlined below:

Table 4 Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	CV Related, resulting from anti-arrythmia loading hospitalization
	Sponsor	Resulting from anti-arrythmia loading hospitalization
Serious	Investigator	SAE
	Sponsor	SAE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

10.2.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB.

[redacted]

10.3 Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device that has been placed on the market.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

Medtronic will notify the regulatory authorities, as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

11. Statistical Design and Methods

This is a feasibility study that is exploratory in nature and with no hypothesis. Therefore, justification on sample size is not required.

11.1 General Aspects of Analysis

[redacted]

11.2 Analysis Execution

Analysis for the LINQ QT Study will occur when data collection has been completed. Analysis will include the primary objective. A final report will be prepared once all data collection has ended and all subjects have completed the study.

11.2.1 Primary Objective #1

The primary objective of the study is to determine if QT changes can be detected from LINQ™/LINQII™ ECG that may occur during and after antiarrhythmic loading. The QT intervals before and after antiarrhythmic loading will be compared for all patients to analyze QT changes that may be caused due to antiarrhythmic drugs.

Analysis Methods: Descriptive summary statistics will be used for this objective.

Determination of Subjects/Data for Analysis: All subjects with data available will be included for this objective.

11.3 Sample Size Determination

There are no sample size requirements as this is an observational study with no hypothesis for the study objective. A sample size of up to 20 enrolled subjects was selected assuming sufficient data can be collected from this cohort to explore the relationship between measured QT intervals from LINQ™/LINQII™ before and after antiarrhythmic drug intake.

11.4 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will undergo screening to confirm eligibility with defined inclusion/exclusion criteria prior to enrollment.
- All sites will use the same version of the Clinical Investigation Plan and electronic case report forms (eCRFs).
- All investigational site personnel and Medtronic personnel will be trained using standardized training materials.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

12. Ethics

12.1 Statement(s) of Compliance

The LINQ QT Study will be conducted according to the Declaration of Helsinki, Clinical Investigation Plan, Good Clinical Practice (GCP) and in accordance to the national and local laws, regulations, standards, and requirements of the countries/geographies in which the study is conducted. The principles of the Declaration of Helsinki are implemented in this study by means of the informed consent process, Ethics

Board approval, study training, and risk benefit assessment. The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the LINQ QT Study.

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent IRB/Ethics Board before initiating a study, continuing review of an ongoing study by an IRB/Ethics Board and obtaining and documenting the freely given informed consent of a subject before initiating the study.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local IRB/Ethics Board Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national, and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to the following:

In the US, the study will be conducted in compliance with:

- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 803: Medical Device Reporting

The study will not begin until IRB/EC approvals/notification, as appropriate, are received.

13. Study Administration

13.1 Monitoring

[redacted]

13.1.1 Monitoring Visits

[redacted]

13.2 Data Management

[redacted]

13.3 Direct Access to Source Data/Documents

The sponsor or a regulatory authority, including the FDA, may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institutions(s) shall allow study related monitoring, audits, IRB/Ethics Board review and regulatory inspection by providing direct access to source data/documents.

13.4 Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic, or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier, such as fluoroscopy images.

13.5 Liability/Warranty/Insurance Information

[redacted]

13.6 CIP Amendments

Approval of the CIP is required from the following groups prior to any study procedures at a study center:

- Medtronic
- An independent Institutional Review Board / Ethics Committee

Similarly, approval of subsequent revisions to the CIP from the above-mentioned groups is required at each study center prior to implementation of the revised CIP at that center.

13.7 Record Retention

13.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to those cited below. All of the below records, with the exception of case history records and case report forms (CRFs), should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB/EC, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports
- Subject's case history records, including:

  [redacted]
- List of investigation sites
- Insurance certificates (if applicable)

- All approved versions of the CIP and Informed Consent Form
- Fully executed Clinical Trial Agreement
- Curriculum Vitae of principal investigator and all co-investigators/sub-investigators
- Documentation of delegated tasks
- Study training records for site personnel involved in the study
- IRB/EC approval documentation, including the IRB/EC composition where required by law, and written information that the investigator or other study staff, when member of the IRB/EC, did not participate in the approval process
- Regulatory authority correspondence, notification, and approval, where required by national legislation
- Any other records that local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

13.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records which include, but are not limited to:

- All correspondence which pertains to the investigation
- Executed Clinical Trial Agreement for all participating sites
- Curriculum vitae (signed and dated as required by local law) of principal investigator and all co-investigators/sub-investigators at participating sites
- Documentation of delegated tasks for all participating sites
- Study training records for site personnel and Medtronic personnel involved in the study
- All approved informed consent versions, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance, if applicable
- Electronically signed and dated eCRFs
- List of names, addresses, telephone numbers and professional position of the clinical investigators and coordinating clinical investigator(s), if appointed
- Names and addresses of the institutions in which the clinical study will be conducted
- Regulatory authority correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors

- Monitoring reports
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the clinical study
- The Clinical Investigation Plan and study related reports, and revisions
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

13.8 Reporting Requirements

13.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events (reported per the country-specific collection requirements), and any deviations from the Clinical Investigation Plan. If any action is taken by an IRB/EC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 5: Investigator reports

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC Approval (either suspension or termination)	Sponsor and Relevant Authorities, if applicable	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Reporting of all other study deviations must comply with IRB/EC policies and/or local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation.
Progress Report	Sponsor and IRB/EC and relevant authorities if applicable	The investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly.
Final Report	Sponsor and IRB/EC and relevant authorities if applicable	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.

13.8.2 Sponsor Reports

Required sponsor reports are listed in Table 6 below.

Table 6: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.
Premature termination or suspension of clinical study	IRB/EC, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB/EC and RAs.

13.9 Publication and Use of Information

Publications from the LINQ QT Study will be handled according to Medtronic's Policies and Standard Operating Procedures and as indicated in the CTA.

13.9.1 Publication Committee

The LINQ QT Study will utilize a Publication Committee which will include the study Principal Investigator, primary Medtronic personnel, and may include additional study investigators. This committee will manage study publications with the goal of publishing findings from the data.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under a separate cover
- Execute the Publication Plan
- Oversee the publication of primary, and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

13.9.2 Management of Primary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary and ancillary publications. Primary publications are those that address analyses of the primary objective as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the primary study objective identified in the Clinical Investigation Plan. They include publications proposed and developed by the Publication Committee, other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with the primary results, other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

13.9.3 Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Decisions regarding authorship and contributor ship will be made by the Publication Committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill ICMJE authorship conditions to be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “Medtronic LINQ QT Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated.

13.9.4 Transparency

Transparency of study results will be maintained by the following means:

- A final report describing the results of all objectives and analysis will be distributed to all investigators and IRBs/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual site’s study data accessible to the corresponding investigator after the completion of the study, if requested

13.10 Suspension or Early Termination

13.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

13.10.2 Early Termination or Suspension

Early Termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

13.10.2.1 Study-wide termination or suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

13.10.2.2 Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g., failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- EC suspension of the study site

- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

13.10.3 Procedures for Termination or Suspension

13.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights, and welfare

13.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights, and welfare

13.10.3.3 IBR/Ethics Committee-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, or legally authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

14. Version History

[redacted]

15. References

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